Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

Etravirine (Intelence, ETR)

(Last updated December 24, 2019; last reviewed December 24, 2019)

Etravirine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Etravirine (ETR) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.[1] ETR was evaluated for carcinogenic potential in mice and rats for up to approximately 104 weeks. Due to intolerance of the formulation, areas under the concentration-time curve (AUC) for ETR were 0.6-fold (in mice) and 0.2-fold to 0.7-fold (in rats) compared to the typical AUC in humans receiving standard dosing. In rats and male mice, no significant findings were noted. In female mice, increased incidences of hepatocellular carcinoma and increased incidences of hepatocellular adenomas or carcinomas combined were observed. It is unclear whether these liver tumor findings in mice are relevant to humans.[1]

Reproduction/Fertility

ETR had no effect on fertility and early embryonic development when tested in pregnant rats at doses that produced systemic drug exposures equivalent to those observed in humans who received the recommended dose of ETR 400 mg per day.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Animal reproduction studies in rats and rabbits revealed no evidence of fetal toxicity or altered development at systemic exposures equivalent to those seen in humans who received the recommended dose of ETR 400 mg per day.[1]

Human Studies in Pregnancy

Pharmacokinetics

ETR pharmacokinetics (PKs) in pregnant women have been reported in two studies. Ramgopal et al. found approximately 1.1-fold to 1.4-fold increases in total ETR AUC, C_{min}, and C_{max} during the second trimester (n = 13) and third trimester (n = 10) compared with levels in the same women postpartum (n = 10). Differences in unbound ETR concentrations were less pronounced, with least-squares mean ratios of approximately 0.9 to 1.2.[2] Similarly, Mulligan et al. found 1.3-fold to 1.9-fold increases in total ETR AUC, C_{min}, and C_{max} during the third trimester (n = 13) compared with levels in the same women postpartum (n = 8).[3] ETR was well tolerated in both of these studies. ETR is a substrate for cytochrome P (CYP) 2C19 metabolism, and the increase in ETR exposure during pregnancy is consistent with the previously observed decrease in CYP2C19 activity during pregnancy.[4]

Placental and Breast Milk Passage

In seven mother-infant pairs, the median ratio of ETR concentration in cord blood to ETR concentration in maternal plasma at delivery was 0.52 (with a range of 0.19–4.25).[3] In another study, the median ratio of cord blood to maternal plasma concentration in 10 mother-infant pairs was 0.32 (with a range of 0.19–0.63).[2] Placental passage of ETR was described in a report on the use of ETR, darunavir/ritonavir, and enfuvirtide in a woman who gave birth to twins. Cord blood ETR levels were 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2 (maternal plasma ETR concentration at delivery was not reported).[5]

Plasma and breast milk concentrations were measured on postpartum Days 5 and 14 in eight women who began taking ETR on postpartum Day 1.[6] Plasma PKs were similar between Days 5 and 14 and were similar to published PK parameters of ETR in nonpregnant adults. ETR $AUC_{0–12h}$ in breast milk was higher in mature milk (collected on Day 14) than in colostrum/transitional milk (collected on Day 5): 12,954 ± 10,200 ng·h/mL versus 4,372 ± 3,016 ng·h/mL ($P = 0.046$). Median ETR concentrations in plasma and breast milk on Day 5 were 300 ng/mL and 241 ng/mL, respectively (within-subject breast milk concentration/plasma concentration ratio was 109%). Median plasma and breast milk concentrations on Day 14 were 197 ng/mL and 798 ng/mL, respectively (within-subject breast milk concentration/plasma concentration ratio was 327%). The maximum ETR concentration in breast milk was significantly higher than the maximum concentration in plasma (1,245 ± 1,159 ng/mL vs. 531 ± 336 ng/mL, $P = 0.04$). Two women had detectable HIV RNA in breast milk on Day 14 despite having suppressed plasma

viral loads. ETR concentrations in the plasma and breast milk of these women were similar to those observed in women with undetectable HIV RNA in breast milk. ETR penetrates well and may accumulate in breast milk.

Teratogenicity/Adverse Pregnancy Outcomes

In eight reported cases of ETR use in pregnancy, no maternal, fetal, or neonatal toxicities were noted.[5,7] One infant was born with a small accessory auricle on the right ear but no other malformations, and no birth defects were noted in the other children.[5] Among the cases of first-trimester ETR exposure that have been reported to the Antiretroviral Pregnancy Registry, one infant with a defect has been noted out of 69 live births; due to this low number of cases to date, no conclusions can be made about risk of birth defects.[8]

Excerpt from Table 8

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Etravirine (ETR) *Intelence*	**Tablets:** • 25 mg • 100 mg • 200 mg For patients who are unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	**Standard Adult Dose:** • ETR 200 mg twice daily with food **Pregnancy** *PKs in Pregnancy:* • PK data in pregnancy suggest 1.2-fold to 1.6-fold increases in ETR exposure during pregnancy. *Dosing in Pregnancy:* • No change in dose indicated.	Placental transfer varies; it is usually in the moderate to high categories, ranging from 0.19–4.25.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key: ARV = antiretroviral; ETR= etravirine; PK = pharmacokinetic

References

1. Etravirine [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022187s025lbl.pdf.
2. Ramgopal M, Osiyemi O, Zorrilla C, et al. Pharmacokinetics of total and unbound etravirine in HIV-1-infected pregnant women. *J Acquir Immune Defic Syndr*. 2016;73(3):268-274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27159225.
3. Mulligan N, Schalkwijk S, Best BM, et al. Etravirine pharmacokinetics in HIV-infected pregnant women. *Front Pharmacol*. 2016;7:239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27540363.
4. Ke AB, Nallani SC, Zhao P, Rostami-Hodjegan A, Unadkat JD. Expansion of a PBPK model to predict disposition in pregnant women of drugs cleared via multiple CYP enzymes, including CYP2B6, CYP2C9 and CYP2C19. *Br J Clin Pharmacol*. 2014;77(3):554-570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23834474.
5. Furco A, Gosrani B, Nicholas S, et al. Successful use of darunavir, etravirine, enfuvirtide and tenofovir/emtricitabine in pregnant woman with multiclass HIV resistance. *AIDS*. 2009;23(3):434-435. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188762.
6. Spencer L, Liu S, Wang C, Neely M, Louie S, Kovacs A. Intensive etravirine PK and HIV-1 viral load in breast milk and plasma in HIV+ women receiving HAART. Poster 891. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, MA.
7. Calcagno A, Trentini L, Marinaro L, et al. Transplacental passage of etravirine and maraviroc in a multidrug-experienced HIV-infected woman failing on darunavir-based HAART in late pregnancy. *J Antimicrob Chemother*. 2013;68(8):1938-1939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23535879.
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2019. Wilmington, NC: Registry Coordinating Center. 2019. Available at: http://www.apregistry.com/.